EXHIBIT 1

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Talc Use, Variants of the *GSTM1*, *GSTT1*, and *NAT2* Genes, and Risk of Epithelial Ovarian Cancer

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Abstract

Epidemiologic evidence suggests a possible association between genital use of talcum powder and risk of epithelial ovarian cancer; however, the biological basis for this association is not clear. We analyzed interactions between talc use and genes in detoxification pathways [*glutathione S-transferase M1* (*GSTM1*), *glutathione S-transferase T1* (*GSTT1*), and *N-acetyltransferase 2* (*NAT2*)] to assess whether the talc/ovarian cancer association is modified by variants of genes potentially involved in the response to talc. Our analysis included 1,175 cases and 1,202 controls from a New England-based case-control study and 210 cases and 600 controls from the prospective Nurses' Health Study. We genotyped participants for the *GSTM1* and *GSTT1* gene deletions and three *NAT2* polymorphisms. We used logistic regression to analyze the main effect of talc use, genotype, and gene-talc interactions in each population and pooled the estimates using a random-effects model. Regular talc use was associated with increased ovarian cancer risk in the combined study population (RR, 1.36; 95% CI, 1.14-1.63; $P_{trend} < 0.001$). Independent of talc, the genes examined were not clearly associated with risk. However, the talc/ovarian cancer association varied by *GSTT1* genotype and combined *GSTM1/GSTT1* genotype. In the pooled analysis, the association with talc was stronger among women with the *GSTT1*-null genotype ($P_{interaction} = 0.03$), particularly in combination with the *GSTM1*-present genotype ($P_{interaction} = 0.03$). There was no clear evidence of an interaction with *GSTM1* alone or *NAT2*. These results suggest that women with certain genetic variants may have a higher risk of ovarian cancer associated with genital talc use. Additional research is needed on these interactions and the underlying biological mechanisms. (Cancer Epidemiol Biomarkers Prev 2008;17(9):2436–44)

Introduction

Genital use of talcum powder has been extensively investigated as a potential risk factor for ovarian cancer. A meta-analysis of 16 previous studies reported an approximately 30% increase in risk of total epithelial ovarian cancer with regular genital exposure to talc (1), and several studies have suggested a stronger association with the serous or serous invasive histologic subtype (2-6). Although the epidemiologic evidence supports a modest association between genital talc use and ovarian cancer risk, the association remains controversial due to the lack of a clear dose-response with increasing frequency or duration of talc use, the possibility of confounding or other biases, and the uncertain biological mechanism.

No prior studies have assessed gene-talc interactions in ovarian cancer risk possibly because little is known about which genes may be involved in the biological response to talc. However, variants of the *glutathione S-transferase M1* (*GSTM1*) and *N-acetyltransferase 2* (*NAT2*) genes appear to modify the association between exposure to asbestos, a known carcinogen that is chemically similar to talc, and risk of malignant mesothelioma (7-10). Talc and asbestos are found together in nature, and before 1976, talcum powder was commonly contaminated with asbestos (9). Although this contamination may have contributed to the risk of ovarian cancer associated with talc use, there is also evidence that talc itself may contribute to carcinogenesis independent of any contamination with asbestos in the past. Talc can induce granulomas and other inflammatory responses *in vivo* (9), and a recent study found that exposing human ovarian stromal and epithelial cells to talc resulted in increased cell proliferation and neoplastic transformation of cells (11). Talc also appears to increase cellular production of reactive oxygen species (11). Interestingly, serous ovarian cancers morphologically resemble peritoneal malignant mesotheliomas (12), suggesting a possible rationale for the stronger association between talc and risk of serous or serous invasive cancers observed in some studies.

Based on similarities between talc and asbestos and the evidence for gene-asbestos interactions in malignant mesothelioma, we examined whether the association between genital talc exposure and ovarian cancer risk is modified by variants of the *NAT2* and *GSTM1* genes as

well as the related *glutathione S-transferase T1* (*GSTT1*) gene. The *GSTM1* and *GSTT1* genes produce enzymes involved in the metabolism of carcinogens and reactive oxygen species (13). These genes are homozygously deleted in approximately 50% (*GSTM1*) and 20% (*GSTT1*) of Caucasians, resulting in complete loss of enzymatic activity (14, 15). The *NAT2* enzyme catalyzes the deactivation of xenobiotics via *N*-acetylation but can also activate certain substrates via *O*-acetylation (16). Individuals with two *NAT2* slow acetylator alleles, approximately 60% of individuals in Caucasian populations, have decreased rates of *N*- and *O*-acetylation (17-20). We hypothesized that the association between talc use and ovarian cancer risk would be stronger among individuals with the *GSTM1*-null, *GSTT1*-null, and *NAT2* slow acetylator genotypes due to decreased metabolism of free radicals and other products of the biological response to talc. We examined these gene-talc interactions, as well as the main effect of talc use and each genotype, in two study populations with a total of 1,385 ovarian cancer cases.

Materials and Methods

New England Case-Control Study. The New England Case-Control Study (NECC) consists of 1,231 epithelial ovarian cancer cases and 1,244 controls from Massachusetts and New Hampshire. Participants were enrolled in the study in two phases: from May 1992 to March 1997 (phase I; 563 cases and 523 controls) or from July 1998 to July 2003 (phase 2; 668 cases and 721 controls). Participants completed a detailed questionnaire on potential risk factors for ovarian cancer and covariates of interest during an in-person interview with a trained interviewer. To avoid capturing changes related to disease status, interviewers asked participants about exposures that occurred at least 1 year before the date of diagnosis for cases or the interview date for controls. The institutional review boards of Brigham and Women's Hospital and Dartmouth Medical School approved both phases of the study, and all participants provided written informed consent.

During the two study phases, NECC researchers identified 2,347 incident cases of ovarian cancer through hospital tumor boards and state cancer registries; 1,845 (79%) of these cases were eligible and 71% of the eligible cases were enrolled in the study. Study investigators identified potential controls using random-digit dialing, drivers' license records, and Massachusetts' town resident lists. Controls were frequency matched to cases by age and state of residence. Of the potentially eligible controls contacted by investigators during phase 1, 68% were eligible and agreed to participate. During phase 2, 197 potential controls declined to be contacted by returning a postcard to ''opt out'' of the study; of the remaining potentially eligible controls who were contacted, 67% were eligible and enrolled in the study. The eligibility criteria and the reasons for nonenrollment of eligible cases are described elsewhere (21).

Over 95% of study participants provided a blood specimen at study enrollment. NECC researchers separated the heparinized blood samples into plasma, RBC, and buffy coat (WBC) components, extracted DNA from the buffy coat using Qiagen DNA extraction, and stored the extracted DNA in freezers at a temperature of -80°C.

Nurses' Health Study. In 1976, 121,701 female registered nurses between ages 30 and 55 years responded to a mailed questionnaire about known and suspected risk factors for disease, leading to the establishment of the Nurses' Health Study (NHS). Study participants completed follow-up questionnaires every 2 years, providing information on new diagnoses of disease and updated information on risk factors. Participation in the study has remained high throughout follow-up; between 1976 and 2004, the percentage of follow-up information obtained (questionnaire responses plus deaths) was 95.3%. The corresponding follow-up percentages for women who provided a WBC or cheek cell specimen were 98% and 99%, respectively. The Institutional Review Board of Brigham and Women's Hospital approved both the NHS and this analysis, and all participants provided implied consent by completing and returning the baseline questionnaire.

In 1989 and 1990, 32,826 participants submitted a blood sample for use in genetic and other biomarker analyses. Details of the blood collection are described elsewhere (22). Between 2001 and 2004, 33,040 women without a blood specimen provided a buccal cell specimen. We used a mouthwash protocol to collect the buccal cell samples, based on evidence that this method provides slightly higher DNA yield and quality, compared with collection using a cytobrush (23). We extracted DNA from each specimen within 1 week of receipt using Qiagen DNA extraction, and stored the DNA at -80°C.

NHS Nested Case-Control Study. We collected information on new diagnoses of ovarian cancer on each questionnaire and also obtained information on deaths due to ovarian cancer through family members, the National Death Index, and the U.S. Postal Service. We confirmed each diagnosis using methods described previously (24). For this analysis, we included all cases with a DNA specimen available from before diagnosis (incident cases) as well as cases who submitted a DNA specimen within 4 years after diagnosis (prevalent cases). We included the prevalent cases in the analysis due to the similarity of characteristics of these cases and the incident cases and also because the interval of 4 years between diagnosis and DNA collection was less than the average survival time of 65.7 months for the incident cases. All cases were diagnosed before June 1, 2004 and had no history of a prior cancer, other than non-melanoma skin cancer.

We randomly selected three controls per case from the study participants who gave a buccal cell or blood specimen, who had not had a bilateral oophorectomy before the date of diagnosis of the matched case, and who had no history of cancer, other than nonmelanoma skin cancer, as of the cycle of diagnosis of the case. We excluded 30 controls from the analysis due to unavailability of genotyping data (*n* = 28) or because the participant was later diagnosed with ovarian cancer and was included in the analysis as a case (*n* = 2). Cases and controls were matched on month and year of birth, DNA type, and menopausal status at diagnosis. For the

blood collection, cases and controls were additionally matched on menopausal status and postmenopausal hormone (PMH) use status at blood draw, month/year and time of day of blood draw, and fasting status at blood draw, because these control selections were also used for analyses of plasma hormones and other biomarkers (25).

Exposure Assessment. The phase 1 and 2 NECC questionnaires included multiple questions about regular use of talcum, baby, or deodorizing powder as an adult. Specific questions asked about type of use (as a dusting powder to the genital area, sanitary napkins, underwear, or nongenital areas), frequency of use, age at first use, number of years used, and brand of powder used. The 1982 NHS questionnaire requested information on whether the participant had ever commonly applied talcum, baby, or deodorizing powder to the perineal area (no, less than once a week, 1-6 times a week, or daily) or to sanitary napkins (yes/no). For this analysis, we defined regular genital talc use as application of powder to the genital/perineal region at least once a week. We also created a categorical variable for frequency of talc use using the categories from the NHS questionnaire.

Genotyping Methods. Genotyping was done at the Dana-Farber/Harvard Cancer Center High Throughput Genotyping Core (for the *NAT2* polymorphisms and NHS *GSTM1* and *GSTT1* gene deletions) and the Molecular Epidemiology Research Laboratory at the Harvard School of Public Health (for the NECC *GSTM1* and *GSTT1* gene deletions). All samples were genotyped for three single nucleotide polymorphisms that identify the *NAT2*5*, *NAT2*6*, and *NAT2*7* alleles. These alleles account for over 99% of slow acetylator alleles in Caucasian populations (16, 26). The *NAT2* I114T (rs1801280), R197Q (rs1799930), and G286E (rs1799931) polymorphisms were genotyped using the 5′-nuclease assay (Taqman) on the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems) in 384-well format. Individuals with two slow acetylator alleles were classified as *NAT2* slow acetylators, whereas individuals with zero or one slow acetylator allele were classified as rapid acetylators.

The NECC samples were genotyped for the *GSTM1* and *GSTT1* gene deletions using multiplex PCR, and the PCR products were resolved on a 1.5% agarose gel. The NHS samples were genotyped for the two gene deletions using Taqman real-time PCR in 384-well format. For both multiplex and real-time PCR assays, individuals were considered to have the *GSTM1*- or *GSTT1*-null genotype if no PCR product was present for the respective gene; all other individuals were classified as *GSTM1*- or *GSTT1*-present.

All DNA samples were whole genome amplified before genotyping. Laboratory personnel blinded to the case-control status of the samples did all genotyping, and each plate included blinded replicate samples for quality-control purposes. The replicate samples were 100% concordant for all genotypes, except the NECC *GSTM1* and *GSTT1* gene deletions, which were 98% and 95% concordant, respectively.

Statistical Analysis. We used a χ^2 test to examine whether the *NAT2* polymorphisms were in Hardy-Weinberg equilibrium in each population and also to examine the distribution of each genotype by case-control status. We conducted all analyses separately in the NHS and NECC populations using consistent exposure and covariate definitions and, after testing for heterogeneity in the results, pooled the estimates using a random-effects model (27). We used conditional (NHS) and unconditional (NECC and NHS) logistic regression to model the multivariable-adjusted odds ratio [as an estimate of the relative risk (RR)] and 95% confidence interval (95% CI) for the main effect of genital talc use, the main effect of each gene, and each combined gene-talc variable. We tested for a linear trend with increasing frequency of talc use by using a continuous variable weighted by the midpoint of each frequency category and calculated the P value for trend using the Wald test. To assess effect modification by genotype, we used unconditional logistic regression to model the association between talc use and ovarian cancer risk within each genotype stratum and calculated the P value for interaction using the χ^2 test for the difference between the log likelihood for models with and without interaction terms between regular genital talc use and genotype. In addition to the analyses of total ovarian cancer, we examined associations with the serous invasive histologic subtype based on evidence from prior studies that risk of this subtype may be more strongly associated with talc use.

We adjusted all analyses for the matching factors, duration of oral contraceptive use, parity, tubal ligation, body mass index (BMI), and duration of PMH use. Women with missing data for the continuous covariates were assigned the median value of the covariate for their study population. In the NHS, where covariate data are available from multiple questionnaire cycles, we used the data from two cycles (2-4 years) before the cycle of diagnosis for each case and their matched controls for consistency with the timeframe of the NECC covariate data. We examined additional covariates as potential confounders, including physical activity, smoking history, menopausal status, age at menopause, breastfeeding duration, and family history of ovarian or breast cancer but did not include them in the final model because they did not substantially change our estimates. We did all analyses using SAS version 9.1 (SAS Institute).

Results

Our study population included 1,175 cases and 1,202 frequency-matched controls from the NECC and 210 cases and 600 matched controls from the NHS for a total of 1,385 ovarian cancer cases and 1,802 controls. Of the NHS cases, 49 were prevalent and 161 were incident with respect to the time of DNA collection. Characteristics of the NHS prevalent and incident cases were generally similar, although a higher percentage of the prevalent cancers were endometrioid (20% versus 9%) and a lower percentage were invasive (76% versus 86%). In the NECC, 618 cases had serous histology (53%), 450 were serous invasive (38%), 153 were mucinous (13%), 172 were endometrioid (15%), and 232 had other/undifferentiated histology (20%). In the NHS, 111 cases were serous (53%), 93 were serous

invasive (44%), 23 were mucinous (11%), 25 were endometrioid (12%), and 51 had other/poorly differentiated histology (24%).

Over 96% of the NECC participants and 98% of the NHS participants were of self-reported European ancestry. In analyses restricted to these participants, the results were similar to those for the entire study population; we therefore included all participants in our analyses to maximize our sample size. The distributions of ovarian cancer risk factors were similar in the NECC and NHS populations, although on average the NHS participants were older, had higher parity, and were more likely to have used PMH in part due to differences in the NECC and NHS age distributions (Table 1). Within each study population, the cases and controls differed with respect to the known risk factors for ovarian cancer. In addition, in the NECC, the cases had higher mean BMI than the controls, and a larger percentage of the cases reported a history of genital talc use. The NHS prevalent and incident cases had similar BMI, tubal ligation history, duration of PMH use, duration of lactation, and genital talc use history; however, the prevalent cases were, on average, slightly younger (60 versus 62 years), were less likely to be postmenopausal (71% versus 87%), and had lower parity (2.7 versus 3.1 children), later age at menarche (13.1 versus 12.5 years), and a longer mean duration of oral contraceptive use (60 versus 41 months; results not shown).

In the NECC, women with a history of regular genital talc use were older, had higher mean BMI, were less likely to have ever used oral contraceptives, were more likely to be postmenopausal, and were more likely to have used PMH (Table 2). Among parous women in the NHS, the mean age at first birth was lower for regular talc users. In addition, NHS participants who regularly used talc were less likely to have a history of smoking or tubal ligation. There was no difference in the genotype frequencies by genital talc use history in either study population.

All P values for the tests for heterogeneity comparing the NECC and NHS results were >0.05. Talc use was associated with increased risk of ovarian cancer in both study populations, although the 95% CIs were wide in the NHS due to the limited sample size (Table 3). In the pooled analysis, the RR for the association with regular genital talc use was 1.36 (95% CI, 1.14-1.63) for total ovarian cancer and 1.60 (95% CI, 1.26-2.02) for the serous invasive subtype. In addition, there were highly significant trends between increasing frequency of talc use and risk of both total and serous invasive ovarian cancer in the NECC (P_{trend} = 0.002 for total and P_{trend} < 0.001 for serous invasive ovarian cancer) and pooled analyses (P_{trend} < 0.001 for both total and serous invasive ovarian cancer). Regular genital talc use was not significantly associated with risk of the endometrioid (RR, 1.41; 95% CI, 0.97-2.05) or mucinous (RR, 1.28; 95% CI, 0.85-1.92) histologic subtypes in the pooled analysis. In the NECC, use of talcum powder on nongenital body areas was unassociated with ovarian cancer risk (multivariable-adjusted RR, also adjusted for genital talc use = 0.91; 95% CI, 0.73-1.12).

Among the controls in each population, the genotype frequencies for the $NAT2$ polymorphisms were in Hardy-Weinberg equilibrium and the distributions of

Table 1. Characteristics of ovarian cancer cases and controls in the NECC and the NHS

Characteristic	NECC			NHS*		
	Cases	Controls	P [†]	Cases	Controls	P [†]
N	1,175	1,202		210	600	
Mean (SD)						
Age (y)[‡]	51 (13)	51 (13)	0.37	62 (8)	62 (8)	0.93
Parity among parous women	2.5 (1.3)	2.8 (1.5)	<0.001	3.0 (1.3)	3.4 (1.5)	0.004
Duration oral contraceptive use (mo)[§]	52 (54)	61 (55)	0.006	46 (42)	53 (49)	0.22
BMI (kg/m²)	26.3 (6.3)	25.7 (5.5)	0.02	25.7 (5.0)	25.7 (4.5)	0.94
Duration PMH use (mo)[§]	78 (86)	74 (71)	0.64	96 (84)	85 (68)	0.18
Duration of lactation (mo)[‖]	5.0 (10.0)	7.3 (13.2)	<0.001	6.0 (10.3)	7.2 (9.7)	0.17
Percent of study population						
Parous	68	81	<0.001	89	93	0.05
Ever user of oral contraceptives	48	60	<0.001	42	45	0.57
History of tubal ligation	14	18	0.007	14	21	0.02
Ever user of PMH	17	20	0.14	71	63	0.02
Family history of ovarian cancer	5.1	2.8	0.004	9.1	3.7	0.002
Any history of genital talc use	29	24	0.003	40	39	0.79
Regular genital talc use (once a week or more)	27	20	<0.001	29	24	0.15
Daily genital talc use	16	12	0.006	18	13	0.08
Genotype frequencies, %						
$GSTM1$ null	51	53	0.42	48	52	0.36
$GSTT1$ null	21	22	0.85	19	21	0.45
$NAT2$ slow acetylator[¶]	63	64	0.74	59	67	0.05

*In the NHS, duration of lactation was collected in 1986, family history of ovarian cancer was first collected in 1992, and history of genital talc use was collected in 1982; for variables collected on multiple questionnaires, the value from two cycles (2-4 y) before the date of diagnosis for each case was used for the case and their matched controls.
[†]P values calculated using proc t test (continuous variables) or a χ^2 test (binary variables).
[‡]Cases and controls in each study population were matched (NHS) or frequency-matched (NECC) on age.
[§]Duration of oral contraceptive use and PMH use among ever users.
[‖]Total duration among parous women.
[¶]$NAT2$ acetylation genotype based on analysis of three single nucleotide polymorphisms, I114T, R197Q, and G286E.

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Table 2. Characteristics of participants in the NECC and the NHS by history of regular genital talc use (at least once a week)

Characteristic	NECC			NHS*		
	No regular talc use	Regular talc use	$P^{\dagger}$	No regular talc use	Regular talc use	$P^{\dagger}$
Mean (SD)						
Age (y)	50 (13)	53 (12)	<0.001	61 (8)	62 (8)	0.64
Parity among parous women	2.7 (1.4)	2.7 (1.4)	0.64	3.2 (1.4)	3.3 (1.5)	0.42
Age at first birth among parous women	25.0 (5.1)	24.6 (4.9)	0.22	25.0 (3.5)	24.4 (3.0)	0.03
Duration oral contraceptive use (mo)‡	58 (55)	54 (54)	0.24	53 (49)	43 (42)	0.08
BMI (kg/m^2)‡	25.7 (5.7)	27.0 (6.4)	<0.001	25.6 (4.6)	26.2 (4.8)	0.13
Duration PMH use (mo)‡	75 (74)	78 (86)	0.68	90 (74)	83 (70)	0.38
Duration of lactation (mo)§	6.4 (12.1)	5.8 (11.5)	0.32	7.2 (10.2)	6.3 (9.6)	0.34
Physical activity (h/wk)	2.8 (5.0)	2.4 (3.8)	0.06	3.0 (2.3)	3.1 (2.4)	0.61
Percent of study population						
Parous	74	75	0.75	93	92	0.81
Ever user of oral contraceptives	55	50	0.03	44	44	0.96
History of tubal ligation	16	16	0.97	22	13	0.008
Postmenopause	45	54	<0.001	81	81	0.86
Ever user of PMH	17	26	<0.001	66	64	0.73
Ever smoker	53	55	0.35	57	47	0.02
Family history of ovarian cancer	3.9	4.1	0.82	4.5	6.4	0.31
Genotype frequencies, %						
GSTM1 null	52	52	0.72	51	49	0.66
GSTT1 null	21	22	0.59	22	17	0.15
NAT2 slow acetylator$^{\parallel}$	63	66	0.23	65	63	0.58

*In the NHS, duration of lactation was collected in 1986, family history of ovarian cancer was first collected in 1992, and history of genital talc use was collected in 1982; for variables collected on multiple questionnaires, the value from two cycles (2-4 y) before the date of diagnosis for each case was used for the case and their matched controls.
$^{\dagger}P$ values calculated using proc ttest (continuous variables) or a χ^2 test (binary variables).
‡Duration of oral contraceptive use and PMH use among ever users.
§Total duration among parous women.
$^{\parallel}NAT2$ acetylation genotype based on analysis of three single nucleotide polymorphisms, I114T, R197Q, and G286E.

the *GSTM1*-null, *GSTT1*-null, and *NAT2* slow acetylator genotypes were consistent with previous reports of Caucasian populations (19, 28, 29). Comparing the prevalent and incident cases in the NHS, a nonsignificantly higher percentage of the prevalent cases were *NAT2* slow acetylators (67% versus 56%), but the *GSTM1* and *GSTT1* genotype distributions did not differ for the prevalent and incident cases (results not shown).

None of the genotypes examined were associated with ovarian cancer risk in the NECC or pooled analyses (Table 4). In the NHS, individuals with the *NAT2* slow acetylator genotype had a significant 35% decrease in ovarian cancer risk (RR, 0.65; 95% CI, 0.45-0.95). The combined *GSTM1*-null/*NAT2* slow acetylator and *GSTT1*-null/*NAT2* slow acetylator genotypes were also inversely associated with risk in the NHS (RR, 0.57; 95% CI, 0.33-0.98 and RR, 0.51; 95% CI, 0.26-0.99, respectively) when compared with the *GSTM1*- or *GSTT1*-present, *NAT2* rapid acetylator genotype. However, these associations were no longer statistically significant when pooled with the NECC estimates.

In analyses stratified by genotype, the association between regular genital talc use and risk of total ovarian cancer was stronger among women with the *GSTT1*-null and combined *GSTM1*-present/*GSTT1*-null genotypes (Table 5). In the pooled analysis, the RR for the association with regular genital talc use was 2.1 (95% CI, 1.4-3.2) for women with the *GSTT1*-null genotype ($P_{\text{interaction}}$ = 0.03) and 2.8 (95% CI, 1.6-5.0) for women with the *GSTM1*-present/*GSTT1*-null genotype ($P_{\text{interaction}}$ = 0.03). The association with the serous invasive subtype was also

stronger within these genotype strata, although the P values for interaction were not statistically significant. The pooled RR was 2.4 (95% CI, 1.4-4.0) for the *GSTT1*-null stratum and 4.8 (95% CI, 2.1-11) for the combined *GSTM1*-present/*GSTT1*-null stratum. The results were consistent in both study populations (results not shown), although the P values for interaction were statistically significant only in the pooled analysis. There was also evidence of a stronger association between regular talc use and risk of serous invasive cancer among women with the *GSTM1*-present genotype, but this interaction was not statistically significant.

We additionally analyzed the association between combined gene-talc variables, compared with a common reference group (wild-type genotype and no talc use), and risk of total and serous invasive ovarian cancer. The results of these analyses were similar to the stratified results presented in Table 5 and are therefore included only as a supplementary table. We also examined interactions between regular genital talc use and combined *GSTM1/NAT2* and *GSTT1/NAT2* genotype (results not shown). The *GSTT1*-null/*NAT2* slow acetylator genotype seemed to increase the risk of total and serous invasive ovarian cancer associated with talc use. However, these analyses were based on small numbers, especially for certain combinations of the genotype and talc variables, and none of the P values for interaction were significant.

In analyses restricted to the NHS incident cases or the NHS cases and controls with a blood specimen, the results were similar to those for the total NHS study population (results not shown).

Table 3. RR (95% CI) for the association between genital talc use and ovarian cancer risk in the NECC and the NHS

	NECC*			NHS*			Pooled [†]
	Cases (%)	Controls (%)	RR (95% CI)	Cases (%)	Controls (%)	RR (95% CI)	RR (95% CI)
Total epithelial ovarian cancer:							
N [‡]	1,175	1,202		210	600		
Regular genital talc use (once a week or more)							
No	859 (73.2)	957 (79.7)	1.00 (reference)	138 (70.8)	414 (76.0)	1.00 (reference)	1.00 (reference)
Yes	314 (26.8)	244 (20.3)	1.40 (1.15-1.70)	57 (29.2)	131 (24.0)	1.24 (0.83-1.83)	1.36 (1.14-1.63)
Frequency of genital talc use							
Never	832 (70.9)	916 (76.3)	1.00 (reference)	120 (61.5)	352 (64.6)	1.00 (reference)	1.00 (reference)
Less than once a week	27 (2.3)	41 (3.4)	0.72 (0.43-1.19)	18 (9.2)	62 (11.4)	0.98 (0.54-1.79)	0.82 (0.55-1.20)
1-6 times a week	123 (10.5)	96 (8.0)	1.33 (1.00-1.79)	22 (11.3)	61 (11.2)	1.01 (0.57-1.79)	1.26 (0.97-1.63)
Daily	191 (16.3)	148 (12.3)	1.41 (1.10-1.79)	35 (18.0)	70 (12.8)	1.44 (0.88-2.37)	1.41 (1.14-1.76)
P_{trend} [§]			0.002			0.18	<0.001
Serous invasive ovarian cancer:							
N [‡]	450	1,202		93	263		
Regular genital talc use (once a week or more)							
No	310 (69.0)	957 (79.7)	1.00 (reference)	60 (68.2)	177 (73.8)	1.00 (reference)	1.00 (reference)
Yes	139 (31.0)	244 (20.3)	1.62 (1.26-2.09)	28 (31.8)	63 (26.3)	1.48 (0.82-2.68)	1.60 (1.26-2.02)
Frequency of genital talc use							
Never	299 (66.6)	916 (76.3)	1.00 (reference)	54 (61.4)	151 (62.9)	1.00 (reference)	1.00 (reference)
Less than once a week	11 (2.4)	41 (3.4)	0.65 (0.32-1.33)	6 (6.8)	26 (10.8)	0.79 (0.29-2.11)	0.70 (0.39-1.24)
1-6 times a week	56 (12.5)	96 (8.0)	1.56 (1.08-2.26)	12 (13.6)	25 (10.4)	1.64 (0.71-3.79)	1.58 (1.12-2.21)
Daily	83 (18.5)	148 (12.3)	1.61 (1.18-2.20)	16 (18.2)	38 (15.8)	1.34 (0.65-2.76)	1.56 (1.17-2.08)
P_{trend} [§]			<0.001			0.29	<0.001

*Unconditional (NECC) and conditional (NHS) logistic regression adjusted for age, study center (NECC only), duration of oral contraceptive use (months), parity (continuous), tubal ligation, BMI (kg/m^2, continuous), and duration of PMH use (months).
[†]P values for tests for heterogeneity comparing the NECC and NHS results were all >0.38.
[‡]Frequencies do not add up to total N due to missing data on talc use.
[§]Weighted by the midpoint of each category of genital talc use frequency and calculated using the Wald test.

Discussion

These results provide additional support for a main effect of genital talc exposure on risk of epithelial ovarian cancer. The presence of a significant trend between frequency of talc use and risk of total and serous invasive ovarian cancer in the NECC and pooled analyses further strengthens the evidence for an association, as most previous studies have not observed a dose response with increasing frequency or duration of talc use (1, 5). The results of our gene-environment analyses suggest that genes in detoxification pathways may be involved in the biological response to talc and that the association between genital talc use and risk of ovarian cancer may vary by genotype. In particular, women with the *GSTT1*-null genotype and the combined *GSTM1*-present/ *GSTT1*-null genotype had a stronger association between talc use and ovarian cancer risk. The evidence for these interactions was consistent in two independent study populations, and the P values for interaction were statistically significant in a pooled analysis of the two populations. However, the direction of the interaction with combined *GSTM1/GSTT1* genotype was unexpected based on the known function of these genes.

Although prior analyses of the talc/ovarian cancer association in the NHS and the NECC have been published, our study includes an additional 612 NECC cases and 679 NECC controls and 8 additional years of follow-up in the NHS (3, 4). In the previous analysis of the NECC, Cramer et al. observed a significant positive association between talc use and risk of both total and serous invasive ovarian cancer. In addition, there was a significant trend with lifetime number of talc applications, after excluding applications during nonovulatory

intervals (P_{trend} = 0.02), but no trend with duration or frequency of talc use (3). In the only prospective study of this association, Gertig et al. reported a significant association between talc use and risk of the serous invasive subtype in the NHS but no association with risk of total ovarian cancer (4). Our findings are consistent with the previous reports for these study populations, although our analysis differs from the prior studies in that we defined our primary exposure variable as genital use of talc at least once per week based on the assumption that habitual talc use is more likely to be recalled accurately and more likely to be associated with ovarian cancer risk. Our findings are also consistent with meta-analyses of this association (1, 30).

The controversy regarding the existence of an association between talc and ovarian cancer has stemmed in part from the lack of a clear mechanism for the association. Although talc and asbestos are chemically similar, their biological effects may differ, because talc does not appear to be a lung carcinogen (31). In addition, it is unclear whether talc applied to the perineum can reach the ovaries, although some studies have shown that inert particles can travel through the female genital tract to the fallopian tubes and ovaries (32, 33), and others have found talc particles in ovarian tissue (34-37). Recent studies have suggested additional potential mechanisms for an association between talc and ovarian cancer. Talc particles can induce an inflammatory response *in vivo*, which may be important in ovarian cancer risk (38). Normal ovarian cells treated with talc are more likely to undergo cell proliferation and neoplastic transformation, and cellular generation of reactive oxygen species increases with increasing exposure to talc (11). Recent studies by Cramer et al. also support the possibility of an

immune-mediated mechanism for an association between talc and ovarian cancer and suggest that exposure of the lower genital tract to talc may be sufficient to cause changes, such as production of heat shock proteins, accumulation of talc in pelvic lymph nodes, or decreased levels of anti-MUC1 antibodies, which could increase ovarian cancer risk (39-41).

Although no prior studies have examined gene-talc interactions, the indication of a possible immune-related mechanism between talc and ovarian carcinogenesis and the evidence for gene-asbestos interactions suggest that genes involved in detoxification and inflammatory pathways could be important in the response to talc. Previous studies have indicated that *NAT2* and *GSTM1* genotype may modify the association between asbestos exposure and risk of malignant mesothelioma; however, not all studies have been consistent (7, 8, 42, 43), and for *NAT2*, the direction of the interaction differed in studies conducted in Finnish and Italian populations (7, 8, 42, 44). This suggests that interactions with these genes may be complex and might depend on additional factors, such as the presence of other gene variants, the type of asbestos, or the level of asbestos exposure (8).

The *GSTM1* and *GSTT1* genes produce enzymes that metabolize products of oxidative stress and catalyze the detoxification of carcinogens and other xenobiotics (45). The *GSTM1* deletion and, to a lesser extent, the *GSTT1* deletion may increase the risk of certain cancers; however, our study and previous analyses do not support a direct association between *GSTM1* or *GSTT1* gene deletion and risk of ovarian cancer (13, 17, 28). Although there is some overlap in GST substrate specificity, there are also differences in the substrates metabolized by the GSTM1 and GSTT1 enzymes, which could help to explain the opposite direction of the interactions we observed between talc use and *GSTM1* and *GSTT1* genotype (13, 17, 45). In studies of pleural malignant mesothelioma, the *GSTM1*-null genotype was associated with increased risk (7, 8, 42, 43) while the *GSTT1*-null genotype was unassociated with risk of malignant mesothelioma (8, 42, 43) but was associated with a significant decrease in risk of asbestosis in one study (46), providing support that some functions of the GSTM1 and GSTT1 enzymes may differ. The direction of the associations between *GSTM1* and *GSTT1* deletions and risk of asbestos-related disease was opposite to the direction of the interactions with talc observed in our study; this could potentially be due to differences in the chemical structures of talc and asbestos or differences in the byproducts produced during the biological response to talc and asbestos. The NAT2 enzyme catalyzes the transfer of an acetyl group to its substrates, including carcinogens such as heterocyclic and aromatic amines, which can result in either activation or deactivation of these substances (17, 20). Approximately 60% of Caucasians have two *NAT2* slow acetylator alleles and consequently have decreased rates of acetylation, which can either increase or decrease the risk of certain cancers depending on the substrate and the cancer site (17, 20). To our knowledge, no previous studies have examined the association between *NAT2* slow acetylator genotype and ovarian cancer risk. We did not observe strong evidence of a main effect of *NAT2* genotype or an interaction between *NAT2* genotype and talc exposure.

Table 4. RR (95% CI) for the association between *GSTM1*, *GSTT1*, and *NAT2* genotype and epithelial ovarian cancer risk in the NECC and the NHS

	NECC*			NHS*			Pooled[†]
	Cases (%)	Controls (%)	RR (95% CI)	Cases (%)	Controls (%)	RR (95% CI)	RR (95% CI)
N[‡]	1,175	1,202		210	600		
GSTM1 genotype							
Present	573 (49.1)	567 (47.4)	1.00 (reference)	102 (52.3)	268 (48.5)	1.00 (reference)	1.00 (reference)
Null	594 (50.9)	628 (52.6)	0.93 (0.79-1.10)	93 (47.7)	285 (51.5)	0.83 (0.58-1.17)	0.91 (0.78-1.06)
GSTT1 genotype							
Present	919 (78.8)	938 (78.5)	1.00 (reference)	157 (81.3)	439 (78.8)	1.00 (reference)	1.00 (reference)
Null	247 (21.2)	257 (21.5)	0.98 (0.80-1.21)	36 (18.7)	118 (21.2)	0.87 (0.57-1.33)	0.96 (0.80-1.16)
NAT2 genotype							
Rapid/intermediate acetylator	387 (36.8)	405 (36.1)	1.00 (reference)	77 (41.0)	182 (33.0)	1.00 (reference)	1.00 (reference)
Slow acetylator	665 (63.2)	717 (63.9)	0.97 (0.81-1.15)	111 (59.0)	369 (67.0)	0.65 (0.45-0.95)	0.82 (0.57-1.20)
Combined *GSTM1/GSTT1* genotype							
Both present	445 (38.2)	430 (36.0)	1.00 (reference)	81 (44.3)	206 (39.2)	1.00 (reference)	1.00 (reference)
M1 null, *T1* present	474 (40.7)	508 (42.5)	0.91 (0.76-1.10)	68 (37.2)	208 (39.5)	0.82 (0.54-1.22)	0.89 (0.75-1.06)
M1 present, *T1* null	128 (11.0)	137 (11.5)	0.94 (0.71-1.24)	17 (9.3)	49 (9.3)	0.98 (0.52-1.84)	0.94 (0.73-1.22)
Both null	119 (10.2)	120 (10.0)	0.94 (0.70-1.26)	17 (9.3)	63 (12.0)	0.65 (0.34-1.24)	0.88 (0.67-1.15)
Combined *GSTM1/NAT2* genotype							
GSTM1 present, *NAT2* rapid	195 (18.6)	188 (16.9)	1.00 (reference)	37 (21.0)	85 (16.4)	1.00 (reference)	1.00 (reference)
GSTM1 null, *NAT2* rapid	189 (18.1)	214 (19.2)	0.82 (0.61-1.09)	35 (19.9)	91 (17.5)	0.96 (0.53-1.74)	0.84 (0.65-1.09)
GSTM1 present, *NAT2* slow	315 (30.1)	343 (30.7)	0.86 (0.66-1.11)	56 (31.8)	161 (31.0)	0.87 (0.51-1.50)	0.86 (0.68-1.09)
GSTM1 null, *NAT2* slow	347 (33.2)	371 (33.2)	0.88 (0.68-1.14)	48 (27.3)	183 (35.2)	0.57 (0.33-0.98)	0.76 (0.50-1.14)
Combined *GSTT1/NAT2* genotype							
GSTT1 present, *NAT2* rapid	296 (28.3)	312 (28.0)	1.00 (reference)	52 (29.7)	144 (27.5)	1.00 (reference)	1.00 (reference)
GSTT1 null, *NAT2* rapid	88 (8.4)	90 (8.1)	1.03 (0.73-1.45)	17 (9.7)	30 (5.7)	1.55 (0.76-3.16)	1.11 (0.81-1.52)
GSTT1 present, *NAT2* slow	519 (49.7)	562 (50.4)	0.97 (0.79-1.19)	90 (51.4)	270 (51.6)	0.87 (0.57-1.33)	0.95 (0.79-1.14)
GSTT1 null, *NAT2* slow	142 (13.6)	152 (13.6)	0.98 (0.74-1.31)	16 (9.1)	79 (15.1)	0.51 (0.26-0.99)	0.76 (0.40-1.43)

*Unconditional (NECC) and conditional (NHS) logistic regression adjusted for age, study center (NECC only), duration of oral contraceptive use (months), parity (continuous), tubal ligation, BMI (kg/m^2, continuous), and duration of PMH use (months).
[†]P values for tests for heterogeneity comparing the NECC and NHS results were all >0.06.
[‡]Frequencies do not add up to total N due to missing genotype data.

Table 5. Pooled RR (95% CI) for the association between regular talc use and ovarian cancer risk, stratified by genotype, in the NECC and the NHS

	All cancers		Serous invasive cancers		Cases and controls in pooled analysis					
					All cases		Serous invasive		Controls	
	Regular talc use		Regular talc use		Regular talc		Regular talc		Regular talc	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Gene/stratum										
GSTM1 genotype										
Present (+)	1.0 (reference)	1.6 (1.2-2.0)	1.0 (reference)	2.0 (1.4-2.8)	480	189	173	90	646	165
Null (-)	1.0 (reference)	1.3 (1.0-1.6)	1.0 (reference)	1.4 (1.0-1.9)	498	179	190	76	690	198
$P_{interaction}$*	0.13		0.08							
GSTT1 genotype										
Present (+)	1.0 (reference)	1.2 (1.0-1.5)	1.0 (reference)	1.5 (1.2-2.0)	785	278	288	129	1,035	301
Null (-)	1.0 (reference)	2.1 (1.4-3.2)	1.0 (reference)	2.4 (1.4-4.0)	194	87	71	38	300	67
$P_{interaction}$*	0.03		0.18							
NAT2 genotype										
Rapid/intermediate acetylator	1.0 (reference)	1.5 (1.1-2.0)	1.0 (reference)	1.9 (1.2-2.8)	330	128	123	57	459	113
Slow acetylator	1.0 (reference)	1.4 (1.1-1.8)	1.0 (reference)	1.6 (1.2-2.1)	552	217	204	96	819	233
$P_{interaction}$*	0.60		0.58							
GSTM1/GSTT1 genotype†										
GSTM1+, GSTT1+	1.0 (reference)	1.4 (1.0-1.8)	1.0 (reference)	1.7 (1.2-2.5)	378	142	136	68	479	140
GSTM1-, GSTT1+	1.0 (reference)	1.2 (0.9-1.5)	1.0 (reference)	1.4 (0.9-1.9)	400	135	151	60	541	154
GSTM1+, GSTT1-	1.0 (reference)	2.8 (1.6-5.0)	1.0 (reference)	4.8 (2.1-11)	98	47	34	22	158	24
GSTM1-, GSTT1-	1.0 (reference)	1.6 (0.9-2.9)	1.0 (reference)	1.4 (0.6-3.1)	94	40	36	16	138	41
$P_{interaction}$*	0.03		0.09							

NOTE: NECC: unconditional logistic regression adjusted for age, study center, duration of oral contraceptive use (months), parity (continuous), tubal ligation, BMI (kg/m², continuous), and duration of PMH use (months); NHS: unconditional logistic regression adjusted for age (months), menopausal status at diagnosis (post, pre/dubious), DNA source, duration of oral contraceptive use (months), parity (continuous), tubal ligation, BMI (kg/m², continuous), and duration of PMH use (months). *P* values for tests for heterogeneity comparing the NECC and NHS results were all >0.36.
*P values for interaction based on likelihood ratio test comparing unconditional logistic regression models with and without gene-talc interaction terms.
†NHS analysis adjusted for age, menopausal status at diagnosis, and DNA source only to improve stability of estimates.

The novelty of this analysis and the assessment of gene-talc interactions in two independent study populations, one with a large number of cases and the other with prospective data on talc use and ovarian cancer incidence, are strengths of this study. However, although the pooled analysis included a large number of cases and controls, our power was still insufficient to detect interactions with certain combinations of genes and for specific histologic subtypes. In addition, although both study populations had extensive covariate data, the use of common exposure and covariate definitions resulted in the loss of some detail particularly for the NECC. Information on talc use was only collected in 1982 in the NHS, so it is possible that some participants were misclassified with respect to their talc use history. However, the number of participants who began using talc after 1982, when the participants were between ages 36 and 61 years, is most likely small. Although we do not have data on age at initiation of talc use in the NHS, in the NECC, approximately 95% of controls with a history of regular genital talc use reported first using talc before age 35 years. Recall or selection bias may have affected the results of the NECC analyses due to the retrospective study design. However, the consistency of the NECC and NHS results suggests that biases related to study design were not a major problem, because, with the exception of the DNA for a subset of the cases, the NHS data were collected prospectively. In addition, the exposure definition of genital talc use at least once a week may have decreased the influence of recall bias in this analysis, because habitual talc use is likely to be recalled more accurately than sporadic use.

In summary, our findings suggest that variants of the *GSTM1* and *GSTT1* genes may modify the association between genital talc use and risk of total and serous invasive ovarian cancer. However, additional research is needed to confirm these findings and to explore potential mechanisms for these interactions particularly for the stronger talc/ovarian cancer association among women with the *GSTM1*-present/*GSTT1*-null genotype. If confirmed, these findings would strengthen the evidence for the carcinogenicity of talc to the ovarian epithelium.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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